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(54) Radiofrequency plasma biocompatibility treatment of medical devices

(57) Polymeric surfaces of medical devices are provided that have enhanced biocompatibility properties. The biocompatibility enhancing agent which contains acid groups is secured to the polymeric substrate by a spacer molecule containing amine groups which is covalently bound to the internal polymeric surface which had been subjected to radiofrequency plasma treatment with a plasma medium of water vapor, oxygen or combination of water vapor and oxygen gas. Internal polymeric surfaces are treated by using a very low pressure plasma medium.

The spacer amine is preferably albumin, urokinase, streptokinase or polyethyleneimine and the biocompatability enhancing agent is preferably heparin, hirudin, hyaluronic acid, streptokinase or urokinase.

The polymeric surface presents an anti-thrombogenic, fibrinolytic or thrombolytic interface with body fluids such as blood flowing through medical device tubing during implantation for medical procedures.

GB 2 257 147 A

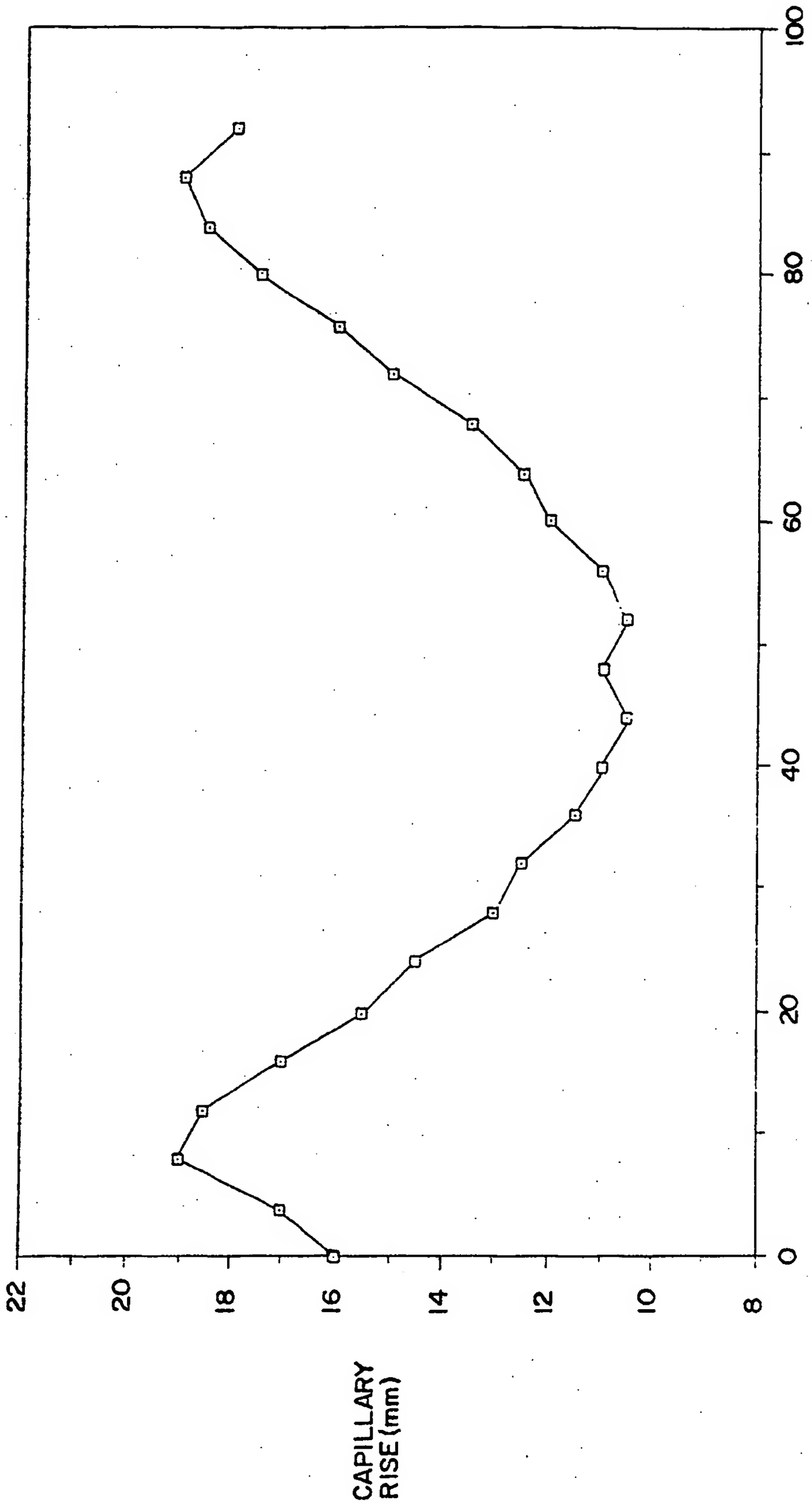
CAPILLARY RISE (mm)
22
20
18
16
14
12
10
8
0
20
40
60
80
100
POSITION (cm)

FIG-1-

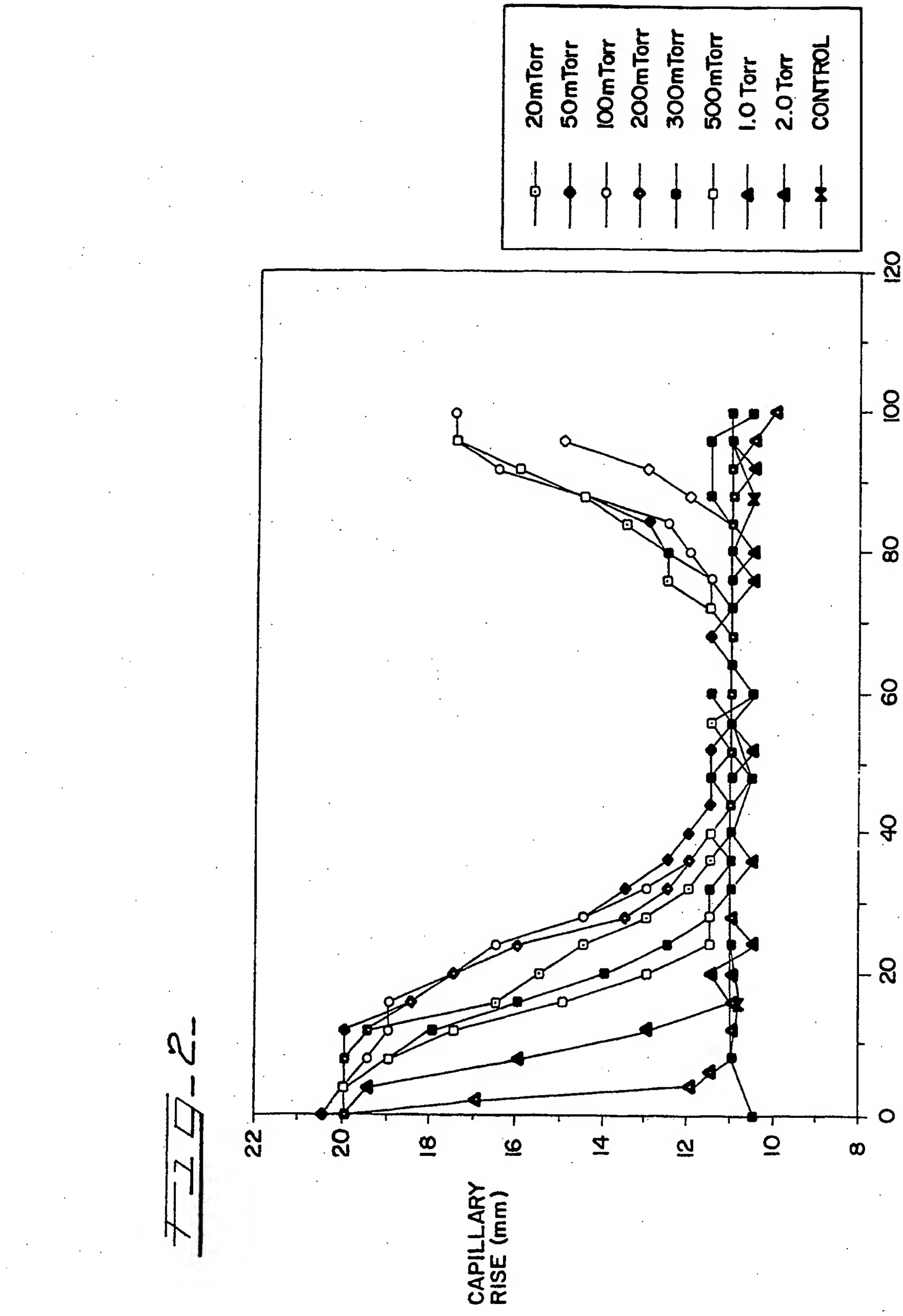
20mTorr
50mTorr
100mTorr
200mTorr
300mTorr
500mTorr
1.0 Torr
2.0 Torr
CONTROL
CAPILLARY RISE (mm)
22
20
18
16
14
12
10
8
POSITION (cm)
0
20
40
60
80
100
120

FIG-2

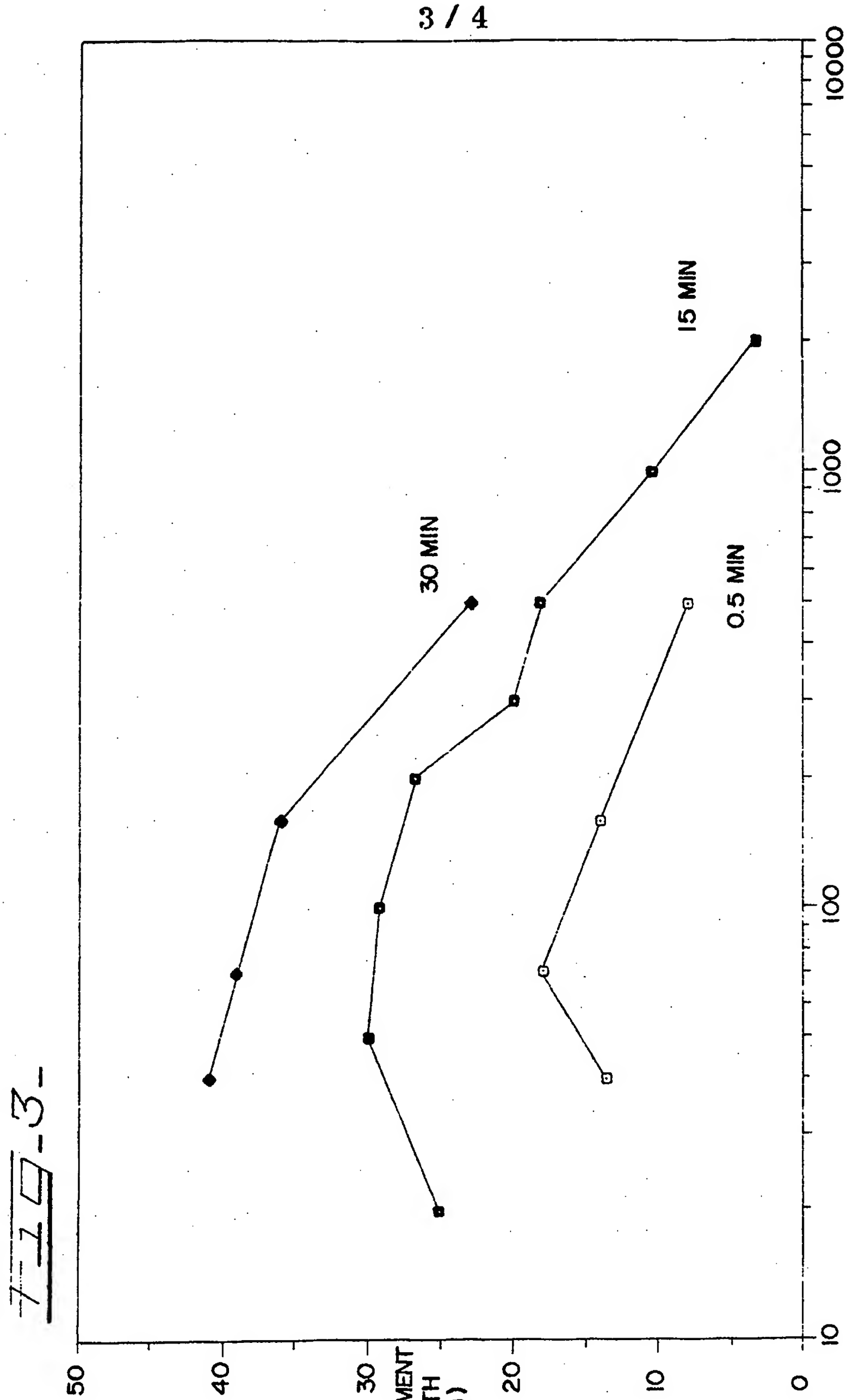
15 MIN
30 MIN
0.5 MIN
OPERATING PRESSURE (m Torr)
10000
1000
100
10
TREATMENT LENGTH (cm)
50
40
30
20
10
0

FIG-3-

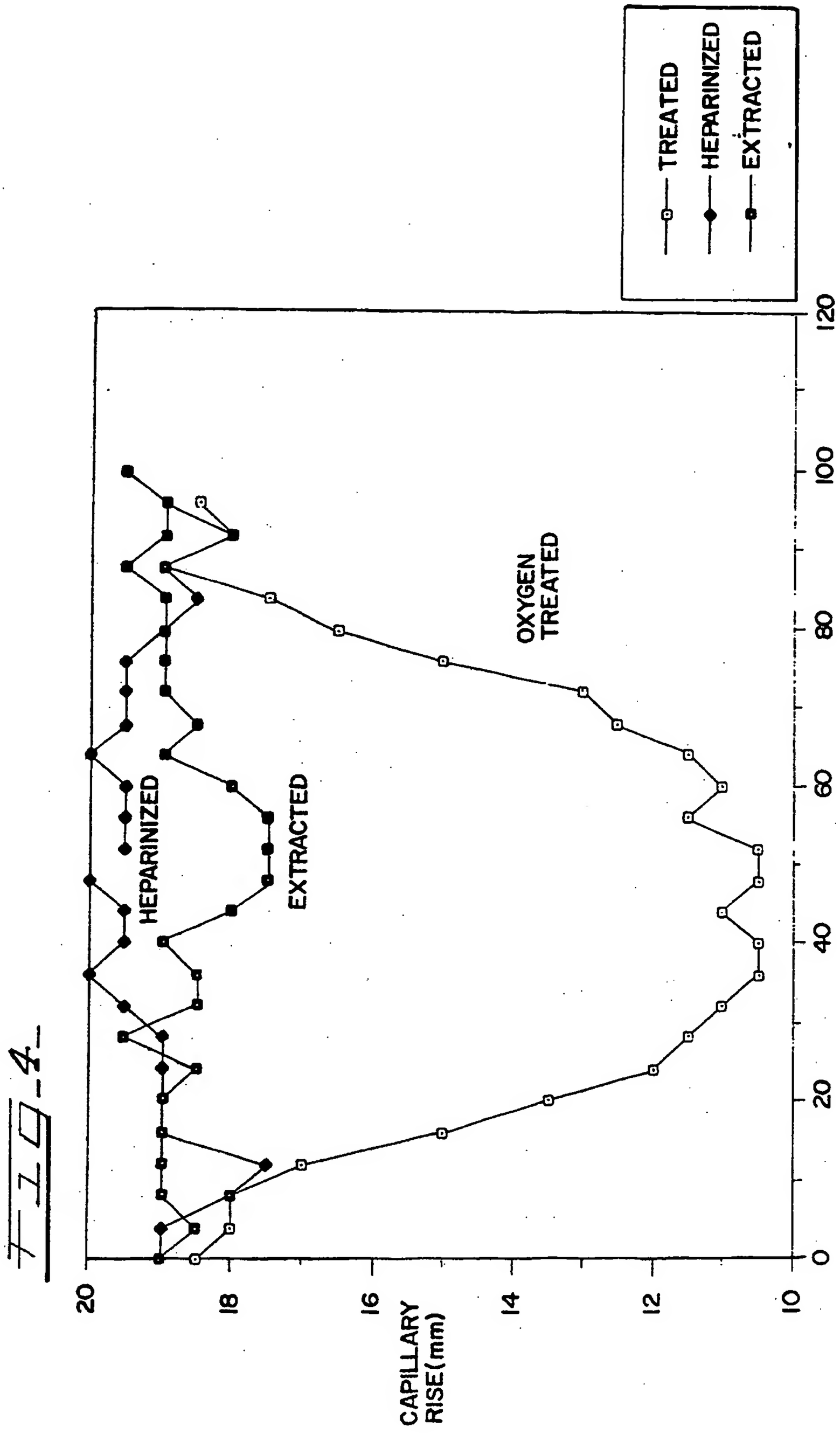
TREATED
HEPARINIZED
EXTRACTED
OXYGEN TREATED
HEPARINIZED
EXTRACTED
120
100
80
60
40
20
0
POSITION (cm)
20
18
16
14
12
10
CAPILLARY RISE(mm)

FIG-4

RADIOFREQUENCY PLASMA BIOCOMPATIBILITY TREATMENT OF MEDICAL DEVICES

The present invention generally relates to enhancing the biocompatibility of polymeric surfaces of medical devices such as the exterior and interior of tubing for catheters and the like. More particularly, the invention relates to surface activation of polymeric surfaces, including lumens of medical-grade tubing, by radiofrequency plasma treatment as a step in achieving immobilization of anti-thrombogenic agents or the like on the polymeric surfaces. The radiofrequency plasma medium includes water vapor, oxygen or combinations thereof. When interior surfaces are treated, the medium is at a substantially low pressure. When this medium is subjected to radiofrequency plasma discharge conditions, the polymeric surfaces of the device being treated, including partially enclosed interior surfaces such as lumens, are activated for attachment thereto of anti-thrombogenic agents such as heparinous materials and the like.

It is well known that many medical devices must have surfaces which are of enhanced biocompatibility. It is also well-known that, generally speaking, biocompatibility properties are enhanced by attempting to secure anti-thrombogenic agents to polymeric surfaces of medical devices, particularly those which are blood-contacting surfaces to be implanted or otherwise used during medical procedures and the like. In many instances, it is particularly undesirable to have the anti-thrombogenic agent leach away in wet environments

such as are encountered by medical devices that engage blood or other body fluids. At times, these surfaces in need of biocompatibility enhancement are partially enclosed interior surfaces such as lumens of catheters or other medical tubing.

Certain attempts have been made and approaches have been suggested whereby a polymeric surface is activated by treatment with a plasma which in turn reacts with heparin or the like to provide a polymeric surface having anti-thrombogenic properties. Included are patents incorporating plasma discharge treatment with a gaseous environment having a variety of gases, including inert gases and organic gases. Patents in this regard include U.S. Patents No. 4,613,517, No. 4,656,083 and No. 4,948,628, which mention a variety of plasma media including those generated from hydrogen, helium, ammonia, nitrogen, oxygen, neon, argon, krypton, xenon, ethylenic monomers and other hydrocarbons, halohydrocarbons, halocarbons and silanes. It will be appreciated that various ones of these plasma media are relatively expensive and can be hazardous to use within a manufacturing environment and/or to dispose of as waste. Also, certain plasma media are more suitable for treatment of specific substrates.

It is desirable to provide a surface treatment procedure which is available for use in connection with rendering anti-thrombogenic any of a number of surfaces of medical devices or the like, in some instances including partially enclosed interior surfaces. It is further desirable that any plasma deposition procedure included in this regard avoid the need to use plasma media that are expensive, potentially hazardous or otherwise difficult to handle. At the same time, any plasma media should strongly bind the anti-thrombogenic agent to the surface being treated, preferably while also accomplishing this in an especially efficient manner that is readily susceptible to use on a large scale.

While certain approaches have been suggested which are particularly designed for treating interior surfaces, these typically require specifically designed equipment and/or are not particularly useful for treating interior surfaces which are spaced a relatively long distance from the access opening to the interior surface. This situation would occur, for example, in attempting to treat a long length of small-diameter tubing such as that for an angiographic or angioplasty catheter, particularly when it is important that entire length of the tubing, including the internal surface at the mid-length of the tubing, is to be treated. In addition to the patents mentioned hereinabove, the following patents describe devices for treating surfaces such as the inside of a tubular body: U.S. Patents No. 4,261,806, No. 4,692,347 and No. 4,846,101.

It has been discovered that plasma media which include a substantial concentration of water vapor, either alone or in combination with oxygen gas, provide an especially advantageous activation of numerous polymeric surfaces that are subjected to radiofrequency plasma treatment conditions in the environment of these media. Plasma media of water vapor or oxygen, either alone or in combination with each other, and when provided at especially low pressures, achieve particularly advantageous activation of partially enclosed interior surfaces such as the lumen of an elongated, small diameter tubing, when the low-pressure plasma medium is subjected to radiofrequency plasma treatment conditions. The thus activated surface is preferably treated with a spacer component having amine moieties, particularly spacer components which have primary or secondary amine groups. An anti-thrombogenic agent or the like, typically with the assistance of a coupling agent, is covalently bound to the spacer component. The result is an evenly covered biocompatible surface that significantly avoids leaching of the anti-thrombogenic agent or the like away from the

device or out of the partially enclosed interior surface such as the tubing lumen.

It is accordingly a general object of the present invention to provide an improved method for treating polymeric surfaces and medical devices or the like having such surfaces with anti-thrombogenic agents or the like immobilized thereon, using radiofrequency plasma discharge techniques, and covalently binding anti-thrombogenic agents or the like to polymeric surfaces so that the agents do not leach away in wet in vivo conditions from the improved polymeric surfaces thus produced.

Preferably the present invention renders medical device polymeric surfaces anti-thrombogenic through a process that is relatively independent of the particular surface and the shape or geometry thereof.

Preferably the present invention provides a modified polymeric surface for a medical device component that exhibits biocompatibility over a polymeric surface not treated according to the method of the present invention.

One embodiment of the present invention avoids the need for specifically designed plasma treatment equipment when treating interior polymeric surfaces and provides an improved process for rendering interior surfaces of medical device components, such as narrow tubing, anti-thrombogenic through a process by which the mean free path of the gaseous treatment media generally approximates the dimensions of the interior volume such as the inside of medical grade tubing, whereby the reactive species are able to penetrate

the inside volume of the device before they become deactivated in the gaseous phase.

These and other objects, features and advantages of this invention will be clearly understood through a consideration of the following detailed description.

The present invention is particularly suitable in connection with the treatment of medical device articles, including those having interior surfaces which are not easily contacted, such as mid-length interior surfaces of medical device tubing having an especially small internal diameter. Specific medical device articles which are advantageously treated according to the invention include catheters, cannulas, balloons for use on catheters including angioplasty balloon catheters and the like and any other devices having operational requirements and properties that can be improved by attaching an anti-thrombogenic, fibrinolytic or thrombolytic agent to one or more surfaces of the device. Typically these types of devices or at least surfaces thereof are made of polymeric materials. In the event that the surface to be treated in accordance with this invention is made of some other material, a thin layer of a suitable polymeric material first can be applied to the surface to be treated.

Polymers which are suitable for use as the surface to be modified with an anti-thrombogenic agent or the like in accordance with the present invention include various polyurethane components such as polyurethanes and polyurethane copolymers such as Pellethane polymers. Included are polyurethane-polyester copolymers, polyurethane-polyether copolymers and nylon-polyether copolymers such as Vestamid polymers. Other polymers which can be treated according to the invention include Silastic (silicon rubber), nylons and other polyamides, nylon-polyester copolymers, polyolefins such as high density polyethylene and the like. The selected polymer

must have overall properties which, except for thrombus concerns, render the polymers suitable for the surface of a medical device made in accordance with the present invention.

In accordance with the invention, these types of polymeric surfaces are made more suitable for long-term or short-term contact with flowing blood or other body fluids. This is accomplished by attaching an anti-thrombogenic agent, fibrinolytic agent or thrombolytic agent to the surface or device. These agents are used in relatively small amounts, and they are attached in such a manner that they remain biologically active, while at the same time being affixed to the polymeric surface in so secure a manner that the agents will not leach away in wet *in vitro* or *in vivo* environments.

Securement of the anti-thrombogenic agent or the like onto the polymeric surface includes positioning the tubing or the like having the polymeric surface within an apparatus to provide a radiofrequency plasma discharge environment. Devices for providing such an environment are generally known in the art. Typical devices in this regard are shown, for example, in U.S. Patents No. 4,632,842 and No. 4,656,083, the subject matter thereof being incorporated by reference hereinto. In devices used according to this invention, a reactor chamber is provided, and the device having the surface to be treated is simply inserted into the chamber without requiring any special structures or positioning. Especially when interior surfaces are to be treated, the chamber is evacuated by a suitable vacuum pump or the like, typically to a pressure below the treatment pressure targeted for the radiofrequency plasma discharge.

A source of fluid which provides the plasma environment then is fed into the chamber, and the desired treatment pressure for the plasma medium is developed and/or maintained. Glow discharge is induced within the reactor chamber by an electrode assembly disposed about

the chamber. For example, when the chamber is generally cylindrically shaped, the electrode assembly can include a pair of band electrodes that are mounted on a traveling block which moves along a desired length of the reactor chamber. The electrode assembly can include instead a radiofrequency coil or the like. After the flow of treating medium or fluid has been established, such as at the desired pressure, discharge is initiated by generating a radiofrequency electric field within the reactor chamber, thereby inducing treatment of the polymeric surface. The radiofrequency electric field can be applied to the chamber either capacitively or inductively.

In accordance with the present invention, the treating fluid or plasma medium is provided within the chamber. When the radiofrequency electric field is applied to this plasma medium, reactive species are created. The reactive species, when they encounter the polymeric surface, react with atoms and/or molecules of the polymeric material, thereby modifying the chemical nature of the surface. It is believed that the polymeric surface is modified by causing the formation of carboxyl groups and/or hydroxyl groups on the surface of the polymeric material. Even an interior polymeric surface will thus be treated, provided the needed low pressure conditions are maintained.

With more particular reference to the treating fluid or plasma medium, air or other gas is first evacuated from the radiofrequency treatment chamber until virtually no air or other gas remains therewithin. Then the water vapor or oxygen is pumped or otherwise injected into the chamber. It is also possible to mix the oxygen with the water and/or water vapor, which can further enhance the efficiency of the surface modification carried out in accordance with this aspect of the invention. The atmosphere within the chamber can be 100% water vapor based upon the total volume of the fluid within the chamber. When water vapor and oxygen are mixed, the

mixture can have as low as about 40% by volume of water vapor. When water vapor and oxygen are included in the plasma gas within the chamber, the preferred volume of water vapor is between about 40 and about 90 volume percent, with the balance being oxygen. It will be appreciated by those familiar with plasma discharge techniques that these volume percents are as present within the chamber at any instant in time because these are flowing fluids.

Concerning the treating fluid or plasma medium to be maintained during radiofrequency plasma surface modification of narrow internal surfaces, the pressure should not exceed about 0.033 kPa (0.25 Torr), typically less than about 0.027 kPa (0.2 Torr). Generally speaking, the water vapor and/or oxygen plasma gas pressure will be no lower than 1.3 Pa (0.01 Torr). Preferably, the treatment pressure should be maintained below about 0.013 kPa (0.1 Torr). At these reduced pressures, an average gaseous molecule will travel longer before it encounters another gaseous molecule. In gaseous kinetics, this is referred to as the mean free path. This longer mean free path at reduced pressures results in increased diffusion length of the reactive species, as well as of other species in the plasma species. If the dimension of a confined volume, such as the diameter of a tubing, is comparable to the mean free path of the reactive species, there is a much higher probability that the reactive species entering within the interior surface will collide with the wall of the device rather than undergo a gas phase collision. These wall collisions cause the inside surface to be chemically functionalized as required by the present invention.

These specific conditions can be used to deposit thin films on the inside surfaces using depositing monomers as plasma media. By the procedure according to the invention, the internal surfaces or lumens of tubings having an internal diameter of 1.8 mm (0.072 inch) or lower and a length of up to about 1.2 m (4 feet) is successfully treated.

Often such tubings are used as catheters for diagnostic and interventional purposes. Generally speaking, treatment of tubing of this general size and within uncomplicated equipment is successfully carried out within about 10 to 30 minutes within an operating pressure range of between about 5.3 Pa (0.04 Torr) and about 0.013 kPa (0.1 Torr).

When a polymeric surface such as Silastic (silicone rubber) is to be treated with the water vapor, oxygen or water vapor/oxygen plasma, it is preferred to pretreat the silicone rubber surface. A suitable pretreatment is within an inert gas plasma such as argon and the like. Suitable reactive species are formed thereafter with the water vapor, oxygen or water vapor and oxygen plasma as discussed herein.

The resulting reactive species-modified polymeric surface is then treated with a spacer molecule which provides reactive sites for attachment of the anti-thrombogenic agent or the like thereto and thus to the polymeric surface. Preferred spacer molecules are those which contain primary or secondary amine groups. Exemplary molecules having suitable spacer groups include albumin, streptokinase, urokinase, polyethyleneimine (PEI) and the like, and combinations thereof.

Covalent linkages between the reactive sites (typically carboxyl groups or hydroxyl groups) on the functionalized polymeric surface and the amine groups of the spacer molecule are formed. Generally speaking, the covalent linkages are accomplished by a condensation or trans-esterification reaction therebetween, often while using a suitable coupling agent. Typical coupling agents in this regard include 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), dicyclohexyl carbodiimide (DCC) or other known coupling agents and the like.

The spacer components are typically applied in solution form. For example, a spacer component such as polyethyleneimine can be utilized within a water solution

containing approximately one percent by weight of PEI. Typically, the spacer component will be present at a concentration of between about 1.0 and about 5.0 weight percent, based upon the weight of the spacer solution.

A suitable anti-thrombogenic, fibrinolytic or thrombolytic agent is then covalently bound to the spacer group, also by means of condensation or trans-esterification chemistry. It is preferred that the agent exhibit acid functionality, whereby the carboxyl groups form a covalent linkage with amine groups of the spacer component. The resultant device has an anti-thrombogenic internal surface from which the anti-thrombogenic agent does not readily leach.

Exemplary anti-thrombogenic agents include heparinous components such as heparin, hirudin, heparin-albumin conjugates, hyaluronic acid, and the like. Illustrative fibrinolytic or thrombolytic agents include streptokinase, urokinase, and the like. Combinations of spacer component and of anti-thrombogenic agent or the anti-thrombogenic agent by itself can be used in the anti-thrombogenic agent composition which is attached to the modified polymeric surface having reactive sites. The anti-thrombogenic agent or the like is applied in the form of a solution having between about 10 and about 20 weight percent of anti-thrombogenic, fibrinolytic or thrombolytic agent, based upon the total weight of the composition.

The following examples illustrate the process and product, as well as performance results.

Example 1

Nylon 12 tubing having an inner diameter of 1.4mm (0.055 inch) and a length of 100cm (39 inches) was treated in a tubular radiofrequency plasma reactor. The plasma was created in the tubular chamber by capacitively coupling the RF at one end of the tubular reactor so that the visible part of the plasma was confined to one end of the tubing. Oxygen was the plasma medium. It was present at

a pressure of (0.07 Torr), and the treatment proceeded for 15 minutes at 20 watts of power. A pressure regulator was present at the downstream portion of the device in order to control the flow of gases and to maintain the desired plasma gas pressure within the reactor. Treatment was effective without requiring any specific orientation of the tubing being treated within the reactor. After treatment was completed, the treated tubing was removed from the reactor and tested to determine the extent of treatment throughout the lumen thereof. The (39 inch) tubing was cut into 25 tubing pieces, each 4cm in length. Each length was numbered 1 through 25 starting from one end to the other. Each piece was dipped into a beaker of de-ionized water. The height to which water moved within the lumen of each piece indicated the extent of surface functionalization that enhanced capillary rise when compared with a surface such as one that had not been subjected to any treatment. Thus, each piece of the tubing was able to support a column of water whose height was a function of the surface energy of the inside surface and thus an indication of the degree to which the inside surface had been functionalized by the radiofrequency plasma.

Figure 1 plots the capillary rise for each 4cm length of tubing, the plot being in order along the length of tubing prior to severance and at the time of its treatment. It will be appreciated that Figure 1 indicates there was a gradient of treatment effect from the ends to the center of the tubing. The treatment of even the central-most 4cm lengths was found to be adequate to attach an anti-thrombogenic agent to the lumen thereof.

Example 2

The procedure of Example 1 was substantially repeated at different various operating pressures and under the same one-end plasma arrangement under 20 watts of power. Figure 2 is a plot which indicates the effect

of operating pressure for constant treatment time, plotting capillary rise versus position along the length of tubing prior to severance. The areas which received minimal treatment were at and near the midpoint along the length of the tubing. It will be appreciated from these data that, as the pressure of operation is reduced, the gradient becomes smaller indicating that the treatment length becomes longer. The central areas which received minimal treatment were more extensive or longer at the higher pressures than at the lower pressures, as can be seen in Figure 2. The control plot is of a totally untreated Nylon 12 tube which was subjected to the capillary test.

Example 3

Tests were conducted as described in Example 1, this time varying the operating pressure. The change of treatment length as a function of operating pressure data are reported in Figure 3. In this Figure, the length of the treated tubing at which the capillary rise is 3mm above the control value is plotted as a function of the operating pressure for different treatment times. The control sample had a capillary rise value of 10.3 $\pm$ 0.3mm. The power applied was constant, and three different treatment times were utilized, as reported in Figure 3.

Example 4

Tubing as described in Example 1 was subjected to radiofrequency plasma deposition from an oxygen medium. The treatment was carried out within a commercial reactor, a Model 7104 unit of Branson International Plasma Corporation. This commercial equipment included seven trays, and the tubing was laid upon the trays for treatment according to the invention. The control sample had a capillary rise value of 10.3 $\pm$ 0.3mm. The treatment pressure in the radiofrequency reactor was about 0.03kPa (230 milliTorr). The thus modified tubing was then treated with

a spacer molecule, followed by attachment of heparin. Thereafter, the surface of the tubing, both inside and outside, was stained with toluidine blue dye to check for the presence of heparin. The dye turned purple indicating the presence of heparin. The heparinized surface was extracted in phosphate buffered saline for at least 72 hours to determine whether or not it was bound to the surface. After 72 hours in the phosphate buffered saline, when the heparinized surface was stained with toluidine blue, the change of dye color to purple indicated that heparin was still present on the surface. The presence of heparin was also confirmed by another independent surface analytic technique, namely static secondary ion mass spectroscopy. This illustrates that the bound heparin was immobilized on the surface. The heparinized surface possessed a high surface energy due to the various hydrophilic functional groups in heparin molecule. This was evident in the capillary rise measurements of the heparinized tubing. Figure 4 plots the capillary rise data for the radiofrequency plasma treated sample, as well as for the heparinized sample and the extracted sample. A flat capillary rise profile is evident for the heparinized sample, which indicates that adequate heparin is present even along the middle length of the tubing's lumen. The relatively flat profile for the extracted sample indicates that the heparin was not extracted to any substantial degree.

Example 5

Tubing for use as catheters for diagnostic and interventional purposes was treated as described in Example 1, except for the following differences. The tubing was a nylon-polyester copolymer (Vestamid). The plasma medium was a mixture of water and oxygen at a pressure of (0.090 Torr) 0.012 kPa. The treated surface was heparinized, both on the outside and in the lumen.

Positive test results indicated the immobilization of heparin on both surfaces.

Example 6

High density polyethylene tubing having an internal diameter of 0.051 inch and a length of (12 inches) was treated in a water vapor plasma for 10 minutes at a pressure of (0.1 Torr) and under 20 watts of radiofrequency power. The thus treated tubing was treated both on the outside and within the lumen with heparin. Both surfaces were then tested for the presence of heparin as described in Example 4, the tests positively indicating the presence of heparin.

Example 7

Tubing of the type described in Example 6 was treated in a radiofrequency plasma containing a medium of a mixture of water and oxygen at a pressure of (0.1 Torr). The power supply was set at 20 watts. Heparinization followed, and the heparinized surfaces were tested, thereby indicating the presence of immobilized heparin within the lumen as well as on the outside surface of the tubing.

Example 8

Nylon 12 tubing having the size specified in Example 1 was treated in radiofrequency plasma using the same process conditions as in Example 1. In this Example 8, the two ends of the tubing were looped into 360 degree loops and into an ellipsoidal shape. The treated samples were tested in accordance with the capillary rise techniques discussed hereinabove. The results were comparable to those for straight elongated tubing, thereby indicating that the ends of the tubing need not be straight for the treatment to be effective within the lumen, provided the low pressure processing according to the present invention is achieved. In fact the treatment

effects in the looped and shaped samples were as good as that in straight tubing. This is important in view of the need to treat lumens of catheters which have shapes other than straight tubings. Often catheters have curved portions, especially at their end tip portions.

Example 9

A polyurethane-polyester copolymer surface was subjected to radiofrequency plasma treatment by subjecting same to a radiofrequency electric field in the presence of a water vapor plasma medium. An aqueous solution containing 1% polyethyleneimine and 3 milligrams of PEI per milliliter of ethyldimethylaminopropyl carbodiimide coupling agent was applied to the radiofrequency plasma discharge modified polyurethane surface, and the reaction time for this step was five minutes. The surface was thereafter well rinsed with deionized water and allowed to air dry.

An aqueous solution of heparin and ethyldimethylaminopropyl carbodiimide containing 5 milligrams of heparin per milliliter of solution and 7.5 milligrams of EDC per milliliter of solution at a pH of 3 was then applied to the PEI-treated surface. Treatment proceeded for one hour, the reaction being at room temperature, after which the samples were well rinsed and allowed to dry in order to provide a polymeric surface having an anti-thrombogenic agent secured to its surface.

Example 10

Samples (in triplicate) of polyurethane devices treated in accordance with Example 9 were subjected to *in vitro* testing. Each sample (and a corresponding control) was immersed in five milliliters of phosphate buffered saline solution (PBS) at a pH of 7.4. Each extraction was run for one of the following extraction times: fifteen minutes, thirty minutes, forty-five minutes, one hour, three hours, twenty-four hours, forty-eight hours and

seventy-two hours. Each sample and control was contacted with toluidine blue to determine the presence of heparin. Each of the samples stained purple, which indicates the presence of heparin on the surface of each of them. The intensity of the staining did not vary from the initial samples to those extracted for seventy-two hours. The controls, which were heparinized and extracted in PBS, exhibited no signs of color change upon staining.

Example 11

Samples of substrates treated in accordance with Example 9 were subjected to *in vitro* extraction conditions in 4M guanidine hydrochloride for one hour at room temperature. Other virtually identical samples were not subjected to extraction conditions. The extract was then assayed using a dimethylmethylene blue colorimetric assay which measures the purple shift in the presence of heparin. The extracted samples were also stained with toluidine blue to detect any heparin that might have been present. No heparin concentration was evident in the guanidine extract, which indicates that no heparin was removed by the guanidine. All of the extracted samples stained purple in toluidine blue with no variation in intensity from the non-extracted samples.

Example 12

Samples were made substantially in accordance with Example 9, except radiolabeled heparin was used. The heparin was labeled using ^{99m}Tc. The samples were counted using a gamma counter, and calculations were performed to determine the actual amount of heparin on the surface of the polymer. The counter detected an initial concentration of heparin of from 8 to 10 micrograms per square centimeter. After extraction with human blood plasma at 37°C. for three hours, the heparin concentration was detected at from 5 to 8 micrograms per square centimeter.

Example 13

Samples made in accordance with Example 9 were subjected to enzyme-linked immunosorbent assay testing for AT-III binding. This testing procedure, identified as ELISA, was as follows. Heparin coated samples were incubated in human blood plasma with AT-III. The AT-III binds to the active site of the heparin. Another solution which contained anti-AT-III conjugated with peroxidase was then allowed to incubate. When the excess was rinsed away, the enzyme substrate and chromogen were added which forms an intense color in the presence of the anti-AT-III conjugate. The color change is directly proportional to the active heparin on the surface. By this testing procedure, the biological activity of the covalently bound heparin was evaluated. This testing confirmed that the heparin on the samples was able to bind AT-III, indicating that the immobilized heparin retains its biological activity with an absorbance value well above the background value for this test.

Example 14

Samples made in accordance with Example 9 were subjected to *in vivo* testing using a known method (J.D. Martinson and R.N. Schaap, Transactions American Society for Artificial Internal Organs, Vol. XXVI, 1980, page 284). In this test, the samples, which were catheters coated in accordance with Example 9, were exposed to blood for thirty minutes. The resultant thrombus was quantified gravimetrically, and the results were reported as a function of the exposed surface area. The results indicated that the catheters heparinized in accordance with the present invention were 5.5 times less thrombogenic than the uncoated polyurethane catheters.

Example 15

Several samples of a polyurethane-polyester copolymer in the form of a catheter were loaded into an RF

plasma reactor. The reactor was pumped down to below 1 mtorr, water vapor and oxygen were brought into the reactor until the pressure rose to the 200-400 mtorr range, and an RF power of 20 watts was applied to create a plasma. A number of runs were made, with the plasmas varying from 80% water vapor and 20% oxygen to 50% water vapor and 50% oxygen, as measured by a gas analyzer. The samples were treated for about 20 seconds and heparinized as in Example 9 and stained with toluidine blue.

A second type of sample was treated in the same way as the first ones, except that there was no oxygen brought into the reactor. This sample was heparinized and stained with toluidine blue. A third type of sample was treated with only oxygen plasma, and this sample was heparinized and stained with toluidine blue.

It was found that the sample which was oxygen plasma treated and subsequently heparinized gave a non-uniform staining compared to the water plasma-or water/oxygen plasma-treated samples. Each of the water plasma-and water/oxygen-plasma treated samples showed uniform staining, but the water/oxygen plasma-treated and subsequently heparinized sample showed a more intense staining than the sample treated in water plasma only and heparinized subsequently.

Example 16

A polyurethane-polyether copolymer (Pellethane) substrate was treated with a water/oxygen plasma at a 4:1 ratio following the procedure described in Example 8 and subsequently heparinized as in Example 9. The heparinized sample was tested for covalent binding of heparin with positive results.

Example 17

A nylon-polyether copolymer (Vestamid from Huls) was treated with a water/oxygen plasma as described in Example 15 and heparinized as in Example 9, except that

the PEI in Example 9 was replaced with albumin as the spacer. The plasma blend was varied on a number of samples from 75% water vapor and 25% oxygen to 50% water vapor and 50% oxygen and blends therebetween. The heparinized sample was tested for covalent binding with positive results.

Example 18

A silastic (silicone rubber) tubing was treated in an argon plasma and subsequently treated in a 75% water/25% oxygen plasma. Another sample was treated with a 75% water/25% oxygen plasma without an argon plasma pretreatment. Both samples were heparinized as in Example 9 three weeks after the plasma treatment. The sample which was pretreated in argon plasma before water/oxygen plasma showed a uniform intense staining when tested for the presence of heparin using toluidine blue, while the sample which was not given an argon plasma pretreatment showed a uniform staining, but not as intense as that subjected to the pretreatment. Another Silastic tubing which was treated in an oxygen-only plasma did not show any presence of heparin, even when heparinization was attempted within a few hours of this plasma treatment.

Example 19

A nylon-polyether copolymer substrate was treated in a water/oxygen plasma. The treated surface was coated with a film of PEI as in Example 9. This surface was coated with a film of hyaluronic acid, which is an anti-thrombogenic agent. The coated surface was tested for covalent binding of hyaluronic acid with positive results.

It will be understood that the embodiments of the present invention which have been described are illustrative of some of the applications of the principles of the present invention. Numerous modifications may be

made by those skilled in the art without departing from the true spirit and scope of the invention.

Claims

1. A method for enhancing the biocompatibility of medical device polymeric surfaces, comprising the steps of:

positioning a polymeric surface within a radiofrequency plasma discharge environment;

inserting water vapor into said radiofrequency plasma discharge environment to provide a plasma medium having a substantial volume of water vapor;

subjecting said plasma medium within the environment to a radiofrequency electric field in order to form reactive species within the environment and to have the reactive species react with the polymeric surface to form a modified polymeric surface having reactive sites;

treating said modified polymeric surface with a spacer component having amine groups whereby covalent linkages are formed between the spacer component amine groups and the reactive sites of the modified polymeric surface; and

contacting an anti-thrombogenic, fibrinolytic or thrombolytic agent having acid functionality and biologically active properties with said spacer component-treated modified polymeric surface, so that the medical device polymeric surface exhibits biocompatibility improvements over the polymeric surface which is not treated according to the method, and the biocompatible medical device polymeric surface anti-thrombogenic, fibrinolytic or thrombolytic agent is resistant to extraction in wet *in vivo* conditions.

2. The method in accordance with claim 1, wherein said plasma medium inserting step further includes inserting oxygen gas.

3. A method for enhancing the biocompatibility of interior polymeric surfaces of medical device components, comprising the steps of:

positioning a medical device component having a polymeric surface within a radiofrequency plasma discharge apparatus;

providing a reduced pressure environment within the radiofrequency plasma discharge apparatus, said reduced pressure environment being on the order of 0.033 kPa (0.25 Torr) or less;

inserting into said reduced pressure environment a plasma medium selected from water vapor, oxygen gas, and the combination of water vapor and oxygen gas, said plasma medium having a pressure not greater than about 0.033 kPa (0.25 Torr);

subjecting said plasma medium to a radiofrequency electric field to induce a gas discharge in order to form reactive species within the plasma discharge apparatus and within the partially enclosed interior polymeric surface to form a modified partially enclosed interior polymeric surface which had been modified by the subjecting step;

treating said modified partially enclosed interior polymeric surface with a spacer component having amine groups whereby covalent linkages are formed between the spacer component amine groups and the reactive sites of the modified partially enclosed interior polymeric surface to form a spacer component-treated modified polymeric surface; and

contacting an anti-thrombogenic, fibrinolytic or thrombolytic agent having acid functionality and biologically active properties with the spacer component-treated modified polymeric surface, so that said partially enclosed modified polymeric surface is a biocompatible surface and the anti-thrombogenic, fibrinolytic or thrombolytic agent of the biocompatible surface is resistant to extraction

in wet in vivo conditions.

4. The method in accordance with claim 3, wherein said subjecting step is carried out while said plasma medium has a pressure of less than about 0.01 kPa (0.1 Torr).

5. The method in accordance with any of claims 1-4, wherein said plasma medium includes between about 40 and about 90 volume percent water vapor and between about 10 and about 60 volume percent oxygen, based upon the total volume of the plasma medium.

6. The method in accordance with any of claims 1-4, wherein said plasma includes between about 40 and about 100 volume percent water vapor and between about 0 and about 60 volume percent oxygen, based on the total volume of the plasma medium.

7. The method in accordance with any of claims 1-6, wherein said treating step utilizes a spacer component which is an amine selected from primary amines, secondary amines, or combinations thereof.

8. The method in accordance with any of claims 1-7, wherein the reactive sites formed by the subjecting step include carboxyl groups, hydroxyl groups or combinations thereof.

9. The method in accordance with any of claims 1-8, wherein the treating step is carried out in the presence of a coupling agent.

10. The method in accordance with any of claims 1-9, wherein the contacting step contacts the spacer

component-treated modified polymeric surface with a heparinous component.

11. The method in accordance with any of claims 1-10, wherein the plasma discharge environment is evacuated prior to the water vapor inserting step.

12. The method in accordance with any of claims 1-11, wherein the positioning step is preceded by pretreating a silicone rubber polymeric surface with an inert gas plasma deposition procedure.

13. The method in accordance with any of claims 3-12, wherein the positioning step places a tubing having a lumen as the partially enclosed interior polymeric surface having a diameter of less than about 2.5 mm (0.1 inch) and having a length suitable for use as a catheter for diagnostic or interventional uses.

14. A medical device component having a biocompatible polymeric surface, wherein the biocompatible polymeric surface comprises a surface which has been modified by subjecting the polymeric surface to radiofrequency discharge treatment within a plasma medium having at least about 40 volume percent water vapor, based upon the total volume of plasma medium, followed by treatment with a spacer component having amine groups forming covalent linkages with the polymeric surface which had been subjected to radiofrequency discharge treatment with said plasma medium, after which an anti-thrombogenic, fibrinolytic or thrombolytic agent having acid functionality had contacted and covalently bonded with the spacer component-treated polymeric surface to provide the biocompatible polymeric surface.

15. A medical device component having a biocompatible polymeric surface, wherein the biocompatible polymeric surface comprises a partially enclosed interior polymeric surface which has been modified by subjecting the interior polymeric surface to radiofrequency discharge treatment within a low-pressure plasma medium to provide a treated interior polymeric surface, the plasma medium selected from water vapor, oxygen gas, or the combination of water vapor and oxygen gas, the plasma medium having a pressure of less than about 0.033 kPa (0.25 Torr), followed by treatment of the treated interior polymeric surface with a spacer component having amine groups forming covalent linkages with the treated interior polymeric surface to form a spacer component-treated interior polymeric surface, after which an anti-thrombogenic, fibrinolytic or thrombolytic agent having acid functionality had contacted and covalently bonded with the spacer component-treated interior polymeric surface to provide a biocompatible partially enclosed interior polymeric surface.

16. The medical device component in accordance with claim 15, wherein the component is a length of tubing having an internal diameter of not greater than about 2.5 mm (0.1 inch) and said internal diameter defines a lumen which is the biocompatible partially enclosed interior polymeric surface.

17. The medical device component in accordance with any of claims 14-16, said polymeric surface is a polyurethane, a polyurethane copolymer, a nylon, a polyamide or a silicone rubber polymer.

18. The medical device component in accordance with any of claims 14-17, wherein the medical device component

is a component of a diagnostic catheter, an interventional catheter, a cannula or a medical device balloon catheter.

19. The medical device component in accordance with any of claims 14-18, wherein said covalent linkages between the modified polymeric surface and the spacer component are between carboxyl or hydroxyl groups formed by the radiofrequency discharge treatment on the polymeric surface and primary or secondary amine groups of the spacer component.

20. The medical device component in accordance with claim 19, wherein a covalent linkage is present between primary or second amine groups of spacer component molecules and the acid functionality groups of the anti-thrombogenic, fibrinolytic or thrombolytic agent.

21. The medical device component in accordance with any of claims 14-20, wherein said polymeric surface is a silicone rubber component that been pretreated with an inert gas plasma.

22. The medical device component in accordance with any of claims 14-21, wherein said polymeric surface had been modified with a radiofrequency discharge treatment from said plasma medium which includes at least about 10 volume percent oxygen, based upon the total volume of the plasma medium.

23. The medical device component in accordance with any of claims 14-22, wherein said polymeric surface had been modified with a radiofrequency discharge treatment from said plasma medium which includes between about 40 and about 100 volume percent water

vapor and between about 0 and about 60 volume percent oxygen.

24. A method according to any one of the claims 1-13 substantially as described herein with reference to the accompanying figures.

25. The product of the method of any one of claims 1-13.

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Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: WPI

Search Examiner

MISS D DAVIES

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Documents considered relevant following a search in respect of claims 1-25

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	EP 0348969 A (BECTON DICKINSON COMPANY) use of oxygen in plasma activation	3
X	EP 0124200 A (BECTON DICKINSON COMPANY) use of oxygen in plasma activation	3

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

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